DESIGN AND DEVELOPMENT OF NEUTRACEUTICAL FORMULATIONS USING QBD PPROACH

SYNOPSIS

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1. INTRODUCTION

The word is a portmanteau of the words "nutrition" and "pharmaceutical", was coined in 1989 by Stephen L. Defelice, founder and chairman of the Foundation of Innovation Medicine. Nutraceuticals are products derived from food sources that are purported to provide extra health benefits, in addition to the basic nutritional value found in foods. Depending on the jurisdiction, products may claim to prevent chronic diseases, improve health, delay the aging process, increase life expectancy, or support the structure or function of the body [1, 2, 3, 4, 5, 11, 12].

The reasons for shift towards nutraceuticals are

1. Increasing numbers of consumers, concerned about healthcare costs.
2. Dissatisfied with pharmaceutical agents in promoting health, are turning to nutraceuticals to improve their health and prevent chronic disease.
3. Health care provider recognize the fact that our heavily processed food supply, coming from crops grown with chemical fertilizers, pesticides, herbicides, and often genetically modified seeds, lacks sufficient nutrients necessary for optimum Health.
4. People believing more in prevention than a cure.
5. People who have chronic diseases and have found no solution in allopathic medicines.
6. Economically challenged patients.

With few exceptions, the U. S. Food and Drug Administration (FDA) have not approved nutraceuticals for health benefits or disease prevention; nonetheless, the manufacturers of nutraceuticals have been touting them as health-promoting agents.

Categories based on natural source

- Carbohydrates & Fiber
- Fat & Essential fatty acids
- Protein
- Minerals like Macro-minerals & Trace minerals
- Vitamins
- Water

- Other nutrients like Antioxidants, Phytochemicals & Intestinal bacterial flora Recombinant nutraceuticals.

Are simply natural with no changes to the food. Food contains several natural components that deliver benefits beyond basic nutrition, such as lycopene in tomatoes, omega-3 fatty acids in salmon or saponins in soy.

1.1 They are grouped on the basis of

I. Chemical Constituents

A. Nutrients
B. Herbals
C. Phytochemicals

II. Probiotic Microorganisms

III. Nutraceutical Enzymes

IV. Prebiotics

Non-traditional nutraceuticals

- Fortified nutraceuticals.
- Recombinant nutraceuticals.

Commercial Nutraceuticals

- Dietary supplements
- Functional food
- Medicinal food
- Pharmaceuticals.

1.2 Formulation challenges

- ✓ Tablet Dosage form.
- Botanicals are complex with multiple chemical components, Can contain up to 50 active. ingredients; 70- 90% of the formula can be actives.
- There are no of active ingredients and excipients
- Nature of nutraceutical Ingredients bring challenges related to particle size, flow, compressibility, moisture sensitivity, ingredient interaction, content uniformity and

quality control (QC) testing as Botanicals and extracts can vary based on region the crop was grown, season grown in and other factors.

- Quantity of each ingredient to enable sufficient delivery of the beneficial ingredients , dose size of the active constituent is large hence very less space for excipients in final formulation. -Nutraceutical formulations normally have more actives present in higher weights than pharmaceutical formulas. The limits of dose size typically result in restricted room for excipients. A typical nutraceutical formulation has 70–90% actives with the balance as excipients, whereas traditional pharmaceutical formulations have 70–90% excipients and 10–30% actives. The fewer excipients and variety of actives in the same formulation make it difficult to achieve certain desired outcomes, such as disintegration time, hardness and friability.

Processing challenges: Large variation in heat, light and moisture sensitivity of ingredients within one formula. Example in Probiotic encapsulation technology Conditions that maintain cell viability like,

- Biomaterial selection-natural and synthetic polymers are used; factors to be addressed are:

a. physicochemical properties (chemical composition, morphology, mechanical strength, stability in GI fluids)

b. toxicity assay;

c. Manufacturing and sterilization processes.

- solvent type and
- toxicity and
- Choice of proper technology are of paramount concern.
- A subsequent challenge is to ascertain that the gastro-protected encapsulated probiotics are released in simulated intestinal fluid (SIF) in vitro, a step that must be preceded by development of a standard protocol that simulates conditions prevailing in the GIT.

Pschological challenges: Nutraceuticals manufacturers must first separate the products and treat nutraceuticals differently from functional foods.

- Tailoring products to domestic tastes and preferences. These might include vegetarianism, Halal or Hindu dietary practices, traditional remedies, flavor and formulation preferences reflecting social and cultural diversity, or reluctance to see functional benefits in staple foods.
- Choice of Study Population is difficult. (Based on age, disease condition etc)

Regulatory Challenges

1. Need to furnish adequate information with scientific evidence to prove that the product is safe, reproducible, and therapeutically efficient and whether it offers such effects for a definite period of time, say two or three years.

2. The need is to create a mechanism to prove that the product quality is reproducible, and this mechanism needs to be in place with solid, scientific support experimentally that can be proved using a reliable technique.

3. Certification requirements often apply to excipients as well as active ingredients.

- GMO Free
- Halal
- Kosher
- WADA Compliance (World Anti Doping Agency) country and product specific

4. Registration category/classification

- According to claims and ingredients, the formula may fit into different categories by country.

Pellets are spherical or nearly spherical, free-flowing granules with a narrow size distribution, typically varying between 500 and 1500 μm for pharmaceutical applications. They are generally produced via a pelletization process whereby a powder blend consisting of an API and excipient particles is agglomerated into spherical granules. After being processed, pellets are usually filled into hard gelatin capsules or compressed into tablets. Furthermore, they can be formulated as immediate release dosage form or in sustain drug release over a long duration time or can be coated also to deliver a drug to a specific site of action in the gastrointestinal tract. Pellets

provide the development scientist with a high degree of flexibility during the design and development of oral dosage forms. They can be divided into desired dose strengths without formulation or process changes, and also be blended to deliver incompatible bioactive agents simultaneously or particles with different release profiles at the same site or at different sites within gastrointestinal tract. Pellets provide development of formulation with high degree of flexibility due to free-flowing characteristic. So they are packed easily without any difficulties. The spherical shape and a low surface area to volume ratio of pellets made uniform film coating. Pellets eliminate the dose dumping effect, which gives smoother plasma concentration profile and gradual absorption of drug than tablet, which further decrease the adverse effect of drugs.

Advantages

- They can be divided in to desired dosage strength without process or formulation changes.
- Improve appearance of product.
- Pellets are of small size and have good flowability compare to powder form.
- Ease of handling, such as filling into capsules
- Incorporation of incompatible ingredients in a single dosage form
- Different release profiles at different sites in the Gastrointestinal tract
- Protection against degradation of active ingredients by oxidation or moisture by providing film coating

Disadvantages

- Pellets filling involve capsule filling which can increase the costs
- Tableting of pellets destroy film coating on the pellets.
- The size of the pellets may vary formulation to formulation but usually is in range of 0.05 mm and 2 mm.

1.3 Formulation Aspects

Pelletization techniques are one with promising technique to develop neutraceutical pellet formulations.

1) Drug Layering:
2) Extrusion-Spheronization:
3) Cryopelletization
4) Compression
5) Balling
6) Hot-Melt Extrusion technology (HME)
7) Freeze pelletization
8) Spray-drying and Spray-congealing

Quality by design is A Quality System for managing a product's lifecycle, a regulatory expectation, intended to increase process and product understanding and thereby decrease patient risk, a multifunctional exercise, Design of Experiment (DOE) and Design Space. The Principle Quality by design (QbD) as a) Risk and knowledge-based decisions b) Systematic approaches process development c) Continuous Improvement d) This leads to "capable" processes. Designing for quality and innovation is one of the three universal processes of the Juran Trilogy, in which Juran describes what is required to achieve breakthroughs in new products, services, and processes. While Quality by Design principles have been used to advance product and process quality in industry, and particularly the automotive industry, they have also been adopted by the U.S. Food and Drug Administration (FDA) for the discovery, development, and manufacture of drugs. As stated in the International Conference on Harmonization Harmonized Tripartite Guidance on Pharmaceutical Development, ICH Q8 (R2), "The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product." Several tools are available as guidance issued by FDA such as "Quality Systems Approach to CGMP Manufacturing" that includes ideas such as Quality by Design (QbD) in the development process. This guidance, amongst others, laid the framework for expectations of regulatory reviewers in their examination of client submittal documentation.

Advantages of QbD

- Better understanding of the process.
- Less batch failure.
- More efficient and effective control of change.
- Return on investment / cost savings.

Understanding QbD

- Initial Confusion
- Research and discussion
- Reaching understanding

1.4 PHARMACEUTICAL QUALITY BY DESIGN

The FDA imperative is outlined in its report "Pharmaceutical Quality for the 21st Century: A Risk-Based Approach."(Pharmaceutical Quality for the 21st Century, 2007). In the past few years, the agency has implemented the concepts of QbD into its pre-market processes. The focus of this concept is that quality should be built into a product with an understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks. This is a successor to the "quality by QC" (or "quality after design") approach that the companies have taken up until the 1990s (Process Validation: General Principles and Practices, 2011).

The QbD initiative, which originated from the Office of Biotechnology Products (OBP), attempts to provide guidance on pharmaceutical development to facilitate design of products and processes that, maximizes the product's efficacy and safety profile while enhancing product manufacturability [1,2].

The first step of the QbD process was to establish a Quality Target Product Profile (QTPP) for the core tablets. The second step was to determine the Critical Quality Attributes (CQA) of the core tablets. The third step incorporated a risk assessment exercise to identify the Critical Processing Parameters (CPP). The final step involved drafting an informal Design of Experiments (DOE) to determine optimal settings of the CPP’s for the critical high shear wet granulation process.

A typical process optimization methodology includes a systematic identification of CQAs, CPPs, and a risk assessment to identify the critical selection of key parameters. A plan can then be drawn up, using a statistical design of experiments (DOE), which can be a full- or partial-factorial design, based on the availability of API and the number of runs that can be manufactured. The DOE experiments involve running parameters at high, medium, and low values, as well as running a defined number of control runs at target parameters. By analyzing the data from the DOE runs, a design space can be identified. Knowledge of the design space enables a control strategy to be defined for the manufacture of the product.

QbD DEVELOPMENT PROCESS

- Begin with a target product profile that describes the use, safety and efficacy of the product
- Define a target product quality profile that will be used by formulators and process engineers as a quantitative surrogate for aspects of clinical safety and efficacy during product development.
- Gather relevant prior knowledge about the drug substance, potential excipients and process operations into a knowledge space. Use risk assessment to prioritize knowledge gaps for further investigation. Design a formulation and identify the critical material (quality) attributes of the final product that must be controlled to meet the target product quality profile.
- Design a manufacturing process to produce a final product having these critical materials attributes.
- Identify the critical process parameters and input (raw) material attributes that must be controlled to achieve these critical material attributes of the final product. Use risk assessment to prioritize process. Parameters and material attributes for experimental verification. Combine prior knowledge with experiments to establish a design space or other representation of process understanding.
- Establish a control strategy for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and/or final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment.

  Continually monitor and update the process to assure consistent quality. [3]

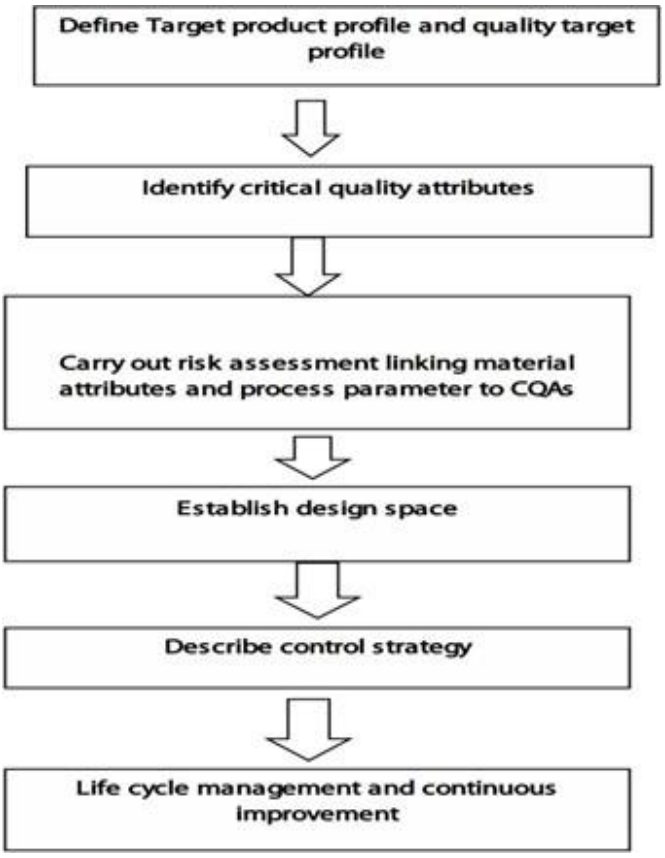
Define Target product profile and quality target profile
Identify critical quality attributes
Carry out risk assessment linking material attributes and process parameter to CQAs
Establish design space
Describe control strategy
Life cycle management and continuous improvement

Figure 1: Flow chart of Qbd

Present work is undertaken to explore optimization of formulation and process parameters used for neutraceutical pellets formulation in pharmaceutical manufacturing with range of its compatibility/reproducibility and requisite supportive data, particularly in the light of an industry's current movement toward submissions based on Design of Experiments (DOE) approach as a part of quality by design QbD [4,5]

2. LITERATURE REVIEW

2.1 Tzankov B et al, (2017) have reported this study; the possibilities for optimization of production process for glimepiride tablets are explored. Direct compression and tableting after granulation in a fluidized bed are examined as suitable and simplified methods for preparation of glimepiride tablets.

2.2 Chaudhari Shilpa P et al, (2017) have reported nutraceuticals: Areview. Nutraceuticals have received considerable interest because of their presumed safety. The Present article focuses on the need for consuming appropriate diets, health issues surrounding failure to adhere to the known healthy eating models, development of new nutraceuticals/functional foods/food supplements with novel health benefits, elucidation mechanisms of action of these products, to define and understand the analytical, formulation and regulatory aspects of nutraceutical. This article may act as a tool to abreast with the recent developments in nutraceutical research.

2.3 Mohamed H. Fayed et al, (2017) have reported high shear wet granulation is a significant component procedure in the pharmaceutical industry. The objective of the study was to investigate the influence of two independent formulation variables; polyvinypyrrolidone (PVP) as a binder (x1) and croscarmellose sodium (ccs) as a disintegrant (x2) on the critical quality attributes of acetaminophen granules and their corresponding tablets using design of experiment (DOE) approach.

2.4 Kane Anil et al, **(2017)** have reported key parameters to be optimized in the development and manufacturing of oral solid-dosage forms have reported it is important to understand the critical processing parameters (CPPS) that impact critical quality attributes (CQA). The CQAS that impact the final outcome (i.e., the therapeutic efficacy of the drug product) usually are parameters such as in-vitro dissolution and drug product stability.

2.5 Nayak Bikash kumar et al, (2016) have reported Quality by design (QBD) approach: tablet compression process optimization using design of experiments study describes an approach to predict tablet properties by multivariate method. In this study, a quality by design approach has been applied to optimize tablet compression process.

2.6 Baishya Himankar et al, (2016) have reported this study was to optimize blending; roller compaction and tablets compression processes using design space approach for a model anti-hyperlipidemic drug fluvastatin. During each processes there are several factors which may affect product quality. So, the main objective of this work was to identify various parameters and

optimize the parameter for formulation of better product which includes blending time, roller force, compression force and machine speed which were recognized as critical process Parameters and were evaluated.

2.7 Ahmed M. Agiba et al, (2014) have reported oral delivery of neutraceutical formulations containing chondroitin sulphate and glucosamine sulphate remains challenge due to excessive first pass hepatic metabolism leads to low oral bioavalability. An oral disintegration Tablet (ODT) was designed to increase the bioavailability and to bypass first pass hepatic metabolism ny oral sublingual route.

2.8 Deb Ratul et al, (2013) have reported Pellets and pelletization techniques: a critical review In the pharmaceutical industry, pellets can be defined as small, free-flowing, spherical particulates manufactured by the agglomeration of fine powders or granules of drug substances and excipients using appropriate processing equipment. Pelletization has gained a great interest in recent years due to its various advantages over other similar techniques; such as uniformity of dose and flexibility in dosage form design. There are a number of pelletization techniques currently used by pharmaceutical industry. Among them Extrusion-spheronization and solution/suspension layering are most commonly used in pharmaceutical industries. Other novel techniques include balling, compression, cryopelletization, dry powder layering, hot melt extrusion etc. In this review, a brief account of all the important techniques with special reference to extrusion-spheronization and solution layering is included.Extrusion–spheronization is a multistep process involving dry mixing, wet granulation, extrusion, spheronization, drying, and screening; whereas solution or suspension layering involves deposition of successive layers of drug and binder solution/ suspension on started seeds, which can be either an inert material or granules of same drug. Every technique has their own advantages and limitations, therefore a thorough understanding of the process variables is important before choosing a pelletization method.

2.9 Brett Justin R et al, (2012) have reported how to improve robustness of a core tablet for a novel modified release oral solid dosage form using quality by design (QbD) principles. The aim of pharmaceutical development is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Several tools are available as guidance issued by FDA such as quality systems approach to CGMP manufacturing.

2.10 Jignyasharavala et al, (2012) have reported aim of the study was to prepare and evaluate bucco-adhesive tablets of rabeprazole sodium that avoid gastric degradation and first pass

metabolism, thereby increasing the drug bioavailability and onset of action. The drug, rabeprazole sodium, belongs to a class of antisecretory compounds.

2.11 Bhasin Rakesh kumar et al, (2012) have reported this study was to design a new orally disintegrating tablet that has high hardness and a fast disintegration rate using conventional tablet technology. Ondansetron was prepared by using traditional technology like direct compression and wet granulation technique. As blend exhibited poor flow in direct compression process, so wet granulation process was finalized. Bitter taste of ondansetron has been masked by use of sweetener like aspartame and peppermint flavor. Quick disintegration has been achieved by use of surfactant in the granulating solvent and superdisintegrant like crospovidone in both intra and extra granular part. Design space has been created by use of different concentrations of both binders as well as disintegrant with the help of doe and a robust formulation has been made.

2.12 Shrivastava Agnivesh et al, (2009) have reported design, optimization, preparation and evaluation of dispersion granules of valsartan and formulation into tablets the present work undertaken was to enhance the solubility and dissolution rate of valsartan a poorly water soluble antihypertensive, by preparation of solid dispersion granules which would additionally allow easy compression in to tablet.

2.13 Patel Rakesh et al, (2009) has reported research work to prepare a sustained release matrix tablet of theophylline. Different grades of hydroxypropyl methyl cellulose were evaluated for gel forming properties. Differential scanning calorimeter (DSC) study shows that drug and other excipients are compatible with each other. The effects of polymers concentration on drug release profile were investigated. A 32 full factorial design was applied to systemically optimize the drug release profile.

2.14 Eutimio Gustavo fernández et al, (2008) have reported was to develop a statistical methodology to optimize tablet manufacturing considering drug chemical and physical properties applying a crossed experimental design. The assessed model drug was dried ferrous sulphate and the variables were the hardness and the relative proportions of three excipients, binder, filler and disintegrant. Granule properties were modeled as a function of excipient proportions and tablet parameters were defined by the excipient proportion and hardness. The desirability function was applied to achieve optimal values for excipient proportions and hardness.

3. AIM AND OBJECTIVE

3.1 AIM

This research work was planned with aim to formulation optimization of neutraceuticals using QbD approach

3.2 OBJECTIVE

1. To extract the neutaceutical from plant origin
2. To design neutraceutical formulations.
3. Development and optimization of formulation and process parameters using statistical tools.

4. PLAN OF WORK

To achieve the set objective, following plan was work out

Literature survey

1. Excipients and neutraceutical selection
2. Extraction of neutraceutical from plant origin
3. Preformulation studies
4. Optimization of excipients
   a) DOE using statistical tools
   b) Effect of excipients and neutraceutical on solid dosage form
   c) Optimization of excipients and neutraceutical.
5. Optimization of Process Parameters
   a) DOE Using Statistical Approach
   b) Effect of Various Process Parameters on formulation dosage form
   c) Optimization of process parameters
6. Evaluation of solid dosage form
   a) Bulk Density
   b) Tapped Density
   c) Cars Compressibility Index
   d) Hausners Ratio
   e) Angle of Repose
   f) Crushing strength
   g) Shape and size of the pellets
   h) % Drug content
   i) In vitro drug release

RATIONALE

- ✓ New molecule is difficult to discover and more expensive and risky than ever before. Many pharmaceutical companies are now trying to manufacture nutraceutical because there is undoubtedly a very huge and growing market. Nutraceuticals cover most of the therapeutic areas, such as anti-arthritic, cold and cough, sleeping disorders, digestion and prevention of certain cancers, osteoporosis, blood pressure, cholesterol control, pain killers, depression and diabetes.
- ✓ Recognition of health benefits from consumption of omega-3 rich seafoods and plant origin is one of the most promising developments in human nutrition and disease prevention research in the past three decades.
- ✓ The potential application of this research work aimed at extraction of neutraceutical the dietary supplement (Omega fatty acid) and formulation design using Design of experiment.
- ✓ In any experimental procedure, several experimental variables or factors may influence the result. A screening experiment using Design of experiment (DOE) is performed in order to determine the experimental variables and interactions that have significant influence on the result, measured in one or several responses.

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